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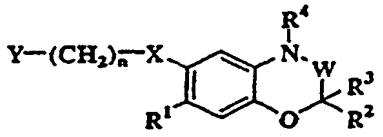
(54) Title: BENZOXAZINE DERIVATIVES



(I)

(57) Abstract

Benzoxazine derivative of the formula (I) in which, R^1 is hydrogen, or a substituent, R^2 and R^3 each independently are hydrogen or C_{1-6} alkyl, R^4 is C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, $C(=Y^1)Z^1R^8$ or $C(=Y^1)R^8$, n is 0 or an integer of 1 to four, W is C=O or $-CH_2-$, X is $-CONH-$, $-CH_2NH-$, $-NHCONH-$ or $-SO_2NH-$, Y is substituted or unsubstituted aryl or heterocyclyl and pharmaceutically acceptable salts thereof are useful as active ingredients for pharmaceutical compositions for curing cardiac insufficiency.

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BENZOXAZINE DERIVATIVES

Technical Field

The present invention relates to benzoxazine derivatives having negative chronotropism, which are used for the treatment of heart failure in mammals inclusive of human being.

Technical Background

Japanese Patent Application Laid-open No. Hei 4-178375, No. Hei 5-70464 and No. Hei 6-220029 have described that the benzoxazine derivatives have a potassium channel activation and are used for the treatment of hypertension and ischemic heart disease such as angina pectoris and myocardial infarction.

However, none of these patents has shown any possibilities of the therapeutic method based on heart rate reduction, for treatment of heart failure.

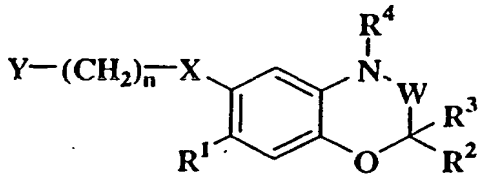
Since heart failure is due to reduction of myocardial contractility, it has been clinically used cardiotonic drugs such as phosphodiesterase inhibitors. However, it is well-known that long-term administration of the cardiotonic drugs worsen life prognosis, because the drugs excessively consume cardiac energy on the basis of positive chronotropic action.

It has been, therefore, desired to develop new drugs which lighten the burden imposed on consumption of cardiac energy by reducing heart rate.

Disclosure of the Invention

As a result of the inventors' intensive study and investigation of benzoxazine derivatives, the inventors have found out that the compounds of the formula (I) have strong bradycardiac activities and are useful as medicines for curing cardiac insufficiency, and they completed the present invention.

The present invention relates to benzoxazine derivatives of the formula (I):



(I)

[in which, R^1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group {said alkyl group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkoxy group {said alkoxy group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a phenyl group (said phenyl group is unsubstituted or substituted by R^6 (said R^6 is a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group)), a formyl group, a cyano group or a nitro group}, a C_{3-6} cycloalkyl group {said cycloalkyl group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a nitro group, a cyano group, a formyl group, a carboxyl group, a hydroxyl group, a formamido group, a cyanamide group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group {said alkylamino group and di C_{1-6} alkylamino group are unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkylcarbonyloxy group, a C_{1-6} alkylurea group, a C_{1-6} alkylthiourea group, an aryl C_{1-6} alkylamino group, a di(aryl C_{1-6} alkyl)amino group, an arylcarbonylamino group, an aryl C_{1-6} alkylcarbonylamino group, an arylsulfonylamino group, an aryl C_{1-6} alkylsulfonylamino group, an aryl C_{1-6} alkylaminocarbonyl group, a di(aryl C_{1-6} alkyl)aminocarbonyl

group, an arylcarbonyl group, an aryl C_{1-6} alkylcarbonyl group, an aryloxycarbonyl group, an aryl C_{1-6} alkyloxycarbonyl group, an arylcarbonyloxy group, an aryl C_{1-6} alkylcarbonyloxy group, an arylurea group, an aryl C_{1-6} alkylurea group, an arylthiourea group or an aryl C_{1-6} alkylthiourea group {said arylalkylamino group, di(arylalkyl)amino group, arylcarbonylamino group, arylalkylcarbonylamino group, arylsulfonylamino group, arylalkylsulfonylamino group, arylalkylaminocarbonyl group, di(arylalkyl)aminocarbonyl group, arylcarbonyl group, arylalkylcarbonyl group, aryloxycarbonyl group, arylalkyloxycarbonyl group, arylcarbonyloxy group, arylalkylcarbonyloxy group, arylurea group, arylalkylurea group, arylthiourea group and aryl alkylthiourean group each are unsubstituted or substituted by R^7 (said R^7 is a halogen atom, a carboxyl group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a C_{1-6} alkoxy group, a phenyl group (said phenyl group is unsubstituted or substituted by R^6), a formyl group, a cyano group or a nitro group)},

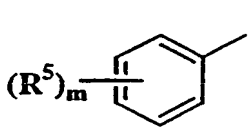
R^2 and R^3 each independently are a hydrogen atom or a C_{1-6} alkyl group {said alkyl group is unsubstituted or substituted by a halogen atom, a C_{1-6} alkoxy group or a hydroxyl group} ,

R^4 is a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group {said alkyl group and cycloalkyl group each are unsubstituted or substituted by R^7} , a phenyl group {said phenyl group is unsubstituted or substituted by R^6}, $C(=Y^1)Z^1R^8$ or $C(=Y^1)R^8$ {Y^1 is a oxygen atom, a sulfur atom, or NR^9 (R^9 is a hydrogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group), Z^1 is a oxygen atom, a sulfur atom or NR^{10} (R^{10} is a C_{1-6} alkyl group), R^8 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkenyl group, a C_{1-6} alkynylgroup, a C_{3-6} cycloalkyl group (said alkyl group, alkenyl group, alkynyl group and cycloalkyl group each are unsubstituted or substituted by R^7) or a phenyl group (said phenyl group is unsubstituted or substituted by R^6)} ,

n is 0 or an integer of 1 to four,

W is C=O or $-CH_2-$,

X is -CONH-, $-CH_2NH-$, -NHCONH- or $-SO_2NH-$,
Y is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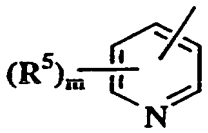
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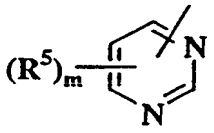
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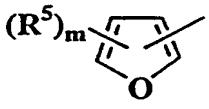
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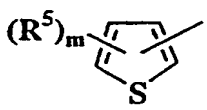
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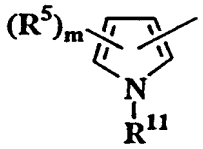
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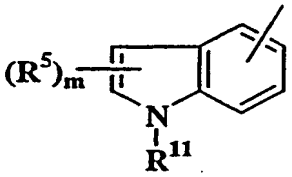
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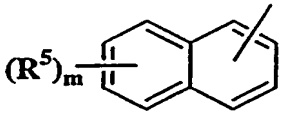
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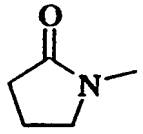
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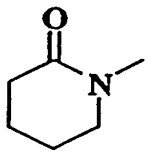
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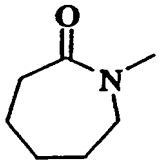
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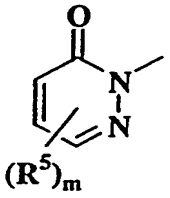

(in which, R^5 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group (said alkyl group is unsubstituted or substituted by a halogen atom or a C_{1-6} alkoxy group), a C_{1-6} alkoxy group (said alkoxy group is unsubstituted or substituted by a halogen atom), a phenyl group (said phenyl group is unsubstituted or substituted by R^6), a hydroxyl group, a nitro group, a cyano group, a formyl group, a formamido group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group, a C_{1-6} alkylcarbonylaminogroup, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkylcarbonyloxy group, a aminosulfonyl group, a C_{1-6} alkylsulfonyl group, a carboxyl group or an arylcarbonyl group,

m is integer of 1 to three, and

R^{11} represents the same meaning as R^{10})}, or its pharmaceutically acceptable salt.

The compound of the present invention has strong activities for reducing heart rate and is useful for improving cardiac functions, and can be used as medicines for curing cardiac insufficiency.

The substituents in the compound of the formula (I) will be explained in more detail hereunder.

In this specification, "n" means normal; "i" means iso; "s" means secondary; "t" means tertiary; "c" means cyclo; "o" means ortho; "m" means metha and "p" means para.

As a halogen atom, a fluorine atom, a chlorine atom, a bromine atom and an iodine atom can be mentioned. Preferable ones are a fluorine atom, a chlorine atom and a bromine atom.

As a C_{1-6} alkyl group, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neopentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, etc. can be mentioned.

Preferable ones are methyl, ethyl, n-propyl, i-propyl and n-butyl.

As a C_{1-6} alkoxy group, methoxy, trifluoromethoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, 1-pentyloxy, 2-pentyloxy, 3-pentyloxy, i-pentyloxy, neopentyloxy, 2,2-dimethylpropoxy, 1-hexyloxy, 2-hexyloxy, 3-hexyloxy, 1-methyl-n-pentyloxy, 1,1,2-trimethyl-n-propoxy, 1,2,2-trimethyl-n-propoxy, 3,3-dimethyl-n-butoxy, etc. can be mentioned.

Preferable ones are methoxy, ethoxy, n-propoxy and i-propoxy.

As a C_{3-6} cycloalkyl group, cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, cycloheptyl, cyclooctyl, etc. can be mentioned.

Preferable ones are cyclopropyl, cyclobutyl and cyclohexyl.

As a C_{1-6} alkylamino group, methylamino, ethylamino, n-propylamino, i-propylamino, c-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, c-butylamino, 1-penthylamino, 2-pentylamino, 3-pentylamino, i-pentylamino, neopentylamino, t-pentylamino, c-pentylamino, 1-hexylamino, 2-hexylamino, 3-hexylamino, c-hexylamino, 1-methyl-n-pentylamino, 1,1,2-trimethyl-n-propylamino, 1,2,2-trimethyl-n-propylamino, 3,3-dimethyl-n-butylamino, etc. can be mentioned.

Preferable ones are methylamino, ethylamino, n-propy amino, i-propylamino and n-butylamino.

As a di C_{1-6} alkylamino group, dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, di-c-propylamino, di-n-butylamino, di-i-butylamino, di-s-butylamino, di-t-butylamino, a di-c-butylamino, di-1-pentylamino, di-2-pentylamino, di-3-pentylamino, di-i-pentylamino, di-neopentylamino, di-t-pentylamino, di-c-pentylamino, di-1-hexylamino, di-2-hexylamino, di-3-hexylamino, di-c-hexylamino, di-(1-methyl-n-pentyl)amino, di-(1,1,2-trimethyl-n-propyl)amino, di-(1,2,2-trimethyl-n-propyl)amino, di-(3,3-dimethyl-n-butyl)amino, methyl(ethyl)amino, methyl(n-propyl)amino, methyl(i-propyl)amino, methyl(c-propyl)amino, methyl(n-butyl)amino, methyl(i-butyl)amino, methyl(s-butyl)amino, methyl(t-butyl)amino, methyl(c-butyl)amino, ethyl(n-propyl)amino, ethyl(i-propyl)amino, ethyl(c-propyl)amino, ethyl(n-butyl)amino, ethyl(i-butyl)amino, ethyl(s-butyl)amino, an ethyl(t-butyl)amino, ethyl(c-butyl)amino, n-propyl(i-propyl)amino, n-propyl(c-propyl)amino, n-propyl(n-butyl)amino, n-propyl(i-butyl)amino, n-propyl(s-butyl)amino, n-propyl(t-butyl)amino, n-propyl(c-butyl)amino, i-propyl(c-propyl)amino, i-propyl(n-butyl)amino, i-propyl(i-butyl)amino, i-propyl(s-butyl)amino, i-propyl(t-butyl)amino, i-propyl(c-butyl)amino, c-propyl(n-butyl)amino, c-propyl(i-butyl)amino, c-propyl(s-butyl)amino, c-propyl(t-butyl)amino, c-propyl(c-butyl)amino, n-

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Preferable ones are dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino and di-n-butylamino.

As a C_{1-6} alkylcarbonylamino group, methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, i-propylcarbonylamino, n-butylcarbonylamino, i-butylcarbonylamino, s-butylcarbonylamino, t-butylcarbonylamino, 1-pentylcarbonylamino, 2-pentylcarbonylamino, 3-pentylcarbonylamino, i-pentylcarbonylamino, neopentylcarbonylamino, t-pentylcarbonylamino, 1-hexylcarbonylamino, 2-hexylcarbonylamino, 3-hexylcarbonylamino, etc. can be mentioned.

Preferable ones are methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, i-propylcarbonylamino and n-butylcarbonylamino.

As a C_{1-6} alkylsulfonylamino group, methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, i-propylsulfonylamino, n-butylsulfonylamino, i-butylsulfonylamino, s-butylsulfonylamino, t-butylsulfonylamino, 1-pentylsulfonylamino, 2-pentylsulfonylamino, 3-pentylsulfonylamino, i-pentylsulfonylamino, neopentylsulfonylamino, t-pentylsulfonylamino, 1-hexylsulfonylamino, 2-hexylsulfonylamino, 3-hexylsulfonylamino, etc. can be mentioned.

Preferable ones are methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, i-propylsulfonylamino and n-butylsulfonylamino.

As a C_{1-6} alkylaminocarbonyl group, methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, i-propylaminocarbonyl, n-butylaminocarbonyl, i-butylaminocarbonyl, s-butylaminocarbonyl, t-butylaminocarbonyl, 1-pentylaminocarbonyl, 2-pentylaminocarbonyl, 3-pentylaminocarbonyl, i-pentylaminocarbonyl,

neopentylaminocarbonyl, t-pentylaminocarbonyl, 1-hexylaminocarbonyl, 2-hexylaminocarbonyl, 3-hexylaminocarbonyl, etc. can be mentioned.

Preferable ones are methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, i-propylaminocarbonyl and n-butylaminocarbonyl.

As a di C_{1-6} alkylaminocarbonyl group, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, di-c-propylaminocarbonyl, di-n-butylaminocarbonyl, di-i-butylaminocarbonyl, di-s-butylaminocarbonyl, di-t-butylaminocarbonyl, di-c-butylaminocarbonyl, di-1-pentylaminocarbonyl, di-2-pentylaminocarbonyl, di-3-pentylaminocarbonyl, di-i-pentylaminocarbonyl, di-neopentylaminocarbonyl, di-t-pentylaminocarbonyl, di-c-pentylaminocarbonyl, di-1-hexylaminocarbonyl, di-2-hexylaminocarbonyl, di-3-hexylaminocarbonyl, etc. can be mentioned.

Preferable ones are dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, di-c-propylaminocarbonyl and di-n-butylaminocarbonyl.

As a C_{1-6} alkylcarbonyl group, methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl, n-butylcarbonyl, i-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, 1-pentylcarbonyl, 2-pentylcarbonyl, 3-pentylcarbonyl, i-pentylcarbonyl, neopentylcarbonyl, t-pentylcarbonyl, 1-hexylcarbonyl, 2-hexylcarbonyl and 3-hexylcarbonyl can be mentioned.

Preferable ones are methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl and the n-butylcarbonyl.

As a C_{1-6} alkoxycarbonyl group, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, t-

butoxycarbonyl, 1-pentyloxycarbonyl, 2-pentyloxycarbonyl, 3-pentyloxycarbonyl, i-pentyloxycarbonyl, neopentyloxycarbonyl, t-penthyloxycarbonyl, 1-hexyloxycarbonyl, 2-hexyloxycarbonyl and 3-hexyloxycarbonyl can be mentioned.

Preferable ones are methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl and t-butoxycarbonyl.

As a C_{1-6} alkylcarbonyloxy group, methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, i-propylcarbonyloxy, n-butylcarbonyloxy, i-butylcarbonyloxy , s-butylcarbonyloxy, t-butylcarbonyloxy, 1-pentylcarbonyloxy, 2-pentylcarbonyloxy, 3-pentylcarbonyloxy, i-penthylcarbonyloxy, neopentylcarbonyloxy, t-pentylcarbonyloxy, 1-hexylcarbonyloxy, 2-hexylcarbonyloxy, 3-hexylcarbonyloxy, 1-methyl-n-pentylcarbonyloxy, 1,1,2-trimethyl-n-propylcarbonyloxy, 1,2,2-trimethyl-n-propylcarbonyloxy, 3,3-dimethyl-n-butylcarbonyloxy, etc. can be mentioned.

Preferable ones are methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, i-propylcarbonyloxy, n-butylcarbonyloxy and t-butylcarbonyloxy.

As the C_{1-6} alkylurea group, methylurea, ethylurea, n-propylurea, i-propylurea, n-butylurea, i-butylurea, s-butylurea, t-butylurea, 1-pentylurea, 2-pentylurea, 3-pentylurea, i-pentylurea, neopentylurea, t-pentylurea, 1-hexylurea, 2-hexylurea, 3-hexylurea, 1-methyl-n-pentylurea, 1,1,2-trimethyl-n-propylurea, 1,2,2-trimethyl-n-propylurea, 3,3-dimethyl-n-butylurea, etc. can be mentioned.

As a C_{1-6} alkylthiourea group, methylthiourea, ethylthiourea, n-propylthiourea, i-propylthiourea, n-butylthiourea, i-butylthiourea, s-butylthiourea, t-butylthiourea, 1-pentylthiourea, 2-pentylthiourea, 3-pentylthiourea, i-pentylthiourea, neopentylthiourea, t-pentylthiourea, 1-hexylthiourea, 2-hexylthiourea, 3-hexylthiourea, 1-methyl-n-pentylthiourea, 1,1,2-trimethyl-n-propylthiourea, 1,2,2-trimethyl-n-propylthiourea and 3,3-dimethyl-n-butylthiourea can be

mentioned.

As a aryl group, a phenyl, biphenylyl, 1-naphthyl, 2-naphthyl, anthryl, phenanthryl, etc. can be mentioned.

Preferable ones are phenyl, biphenylyl, 1-naphthyl and 2-naphthyl.

As a aryl C_{1-6} alkylamino group, benzylamino, o-methylbenzylamino, m-methylbenzylamino, p-methylbenzylamino, o-chlorobenzylamino, m-chlorobenzylamino, p-chlorobenzylamino, o-fluorobenzylamino, p-fluorobenzylamino, o-methoxybenzylamino, p-methoxybenzylamino, p-nitrobenzylamino, p-cyanobnezylamino, phenethyl amino, o-methylphenethylamino, m-methylphenethylamino, p-methylphenethylamino, o-chlorophenethylamino, m-chlorophenethylamino, p-chlorophenethylamino, o-fluorophenethylamino, p-fluorophenethylamino, o-methoxyphenethylamino, p-methoxyphenethylamino, p-nitrophenethylamino, p-cyanophenethylamino, phenylpropylamino, phenylbutylamino, phenylpentylamino, phenylhexylamino, naphthylamino, biphenylylamino, anthrylamino and phenanthrylamino can be mentioned.

Preferable ones are benzylamino, p-methylbenzylamino, phenethylamino, p-methoxyphenethylamino and phenylpropylamino.

As an arylcarbonylamino group, benzoylamino, 1-naphthylcarbonylamino, 2-naphthylcarbonylamino, o-methylbenzoylamino, m-methylbenzoylamino, p-methylbenzoylamino, o-chlorobenzoylamino, p-chlorobenzoylamino, o-fluorobenzoylamino, p-fluorobenzoylamino, o-methoxybenzoylamino, p-methoxybenzoylamino, p-nitrobenzoylamino, p-cyanobenzoylamino, p-phenylbenzoylamino, etc. can be mentioned.

Preferable ones are benzoylamino and p-fluorobenzoylamino.

As an aryl C_{1-6} alkylcarbonylamino group, phenylacetylamino, o-methylphenylacetylamino, m-methylphenylacetylamino, p-

methylphenylacetylamino, o-chlorophenylacetylamino, p-chlorophenylacetylamino, p-fluorophenylacetylamino, o-methoxyphenylacetylamino, p-methoxyphenylacetylamino, p-nitrophenylacetylamino, p-cyanophenylacetylamino, 2-phenylethylcarbonylamino, 3-phenylpropylcarbonylamino, 4-phenylbutylcarbonylamino, 5-phenylpentylcarbonylamino, 6-phenylhexylcarbonylamino, etc. can be mentioned.

Preferable ones are phenylacetylamino and 2-phenylethylcarbonylamino.

As an arylsulfonyl group, benzenesulfonylamino and p-toluenedsulfonylamino can be mentioned.

As an aryl C_{1-6} alkylaminocarbonyl group, benzylaminocarbonyl, o-methylbenzylaminocarbonyl, m-methylbenzylaminocarbonyl, p-methylbenzylaminocarbonyl, o-chlorobenzylaminocarbonyl, p-chlorobenzylaminocarbonyl, o-fluorobenzylaminocarbonyl, p-fluorobenzylaminocarbonyl, o-methoxybenzylaminocarbonyl, p-methoxybenzylaminocarbonyl, p-nitrobenzylaminocarbonyl, p-cyanobenzylaminocarbonyl, phenethylaminocarbonyl, p-methylphenethylaminocarbonyl, p-chlorophenethylaminocarbonyl, p-cyanophenethylaminocarbonyl, 3-phenylpropylaminocarbonyl, 4-phenylbutylaminocarbonyl, 5-phenylpentylaminocarbonyl and 6-phenylhexylaminocarbonyl can be mentioned.

Preferable ones are benzylaminocarbonyl, p-methylbenzylaminocarbonyl, p-chlorobenzylaminocarbonyl, p-fluorobenzylaminocarbonyl and phenethylaminocarbonyl.

As an arylcarbonyl group, benzoyl, p-methylbenzoyl, p-t-butylbenzoyl, p-methoxybenzoyl, p-chlorobenzoyl, p-nitrobenzoyl and p-cyanobenzoyl can be mentioned.

Preferable ones are benzoyl, p-nitrobenzoyl and p-cyanobenzoyl.

As an aryl C_{1-6} alkylcarbonyl group, phenylacetyl, p-

methylphenylacetyl, p-t-butylphenylacetyl, p-methoxyphenylacetyl, p-chlorophenylacetyl, p-nitrophenylacetyl, p-cyanophenylacetyl, phenethylcarbonyl, 3-phenylpropylcarbonyl, 4-phenylbutylcarbonyl, 5-phenylpentylcarbonyl and 6-phenylhexylcarbonyl can be mentioned.

Preferable ones are phenylacetyl and phenethylcarbonyl.

As an aryloxycarbonyl group, phenoxycarbonyl, o-methylphenoxycarbonyl, p-methylphenoxycarbonyl, p-chlorophenoxycarbonyl, p-fluorophenoxycarbonyl, p-methoxyphenoxycarbonyl, p-nitrophenoxycarbonyl, p-cyanophenoxycarbonyl, 1-naphthoxycarbonyl and 2-naphthoxycarbonyl can be mentioned.

As an aryl C_{1-6} alkyloxycarbonyl group, benzyloxycarbonyl, o-methylbenzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-fluorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-cyanobenzyloxycarbonyl, 1-naphthymethoxylcarbonyl, 2-naphthymethoxylcarbonyl and pyridylmethyloxycarbonyl can be mentioned.

As an arylcarbonyloxy group, benzoyloxy, o-methylbenzoyloxy, p-methylbenzoyloxy, p-chlorobenzoyloxy, p-fluorobenzoyloxy, p-methoxybenzoyloxy, p-nitrobenzoyloxy, p-cyanobenzoyloxy, 1-naphthylcarbonyloxy and 2-naphthylcarbonyloxy can be mentioned.

As an aryl C_{1-6} alkylcarbonyloxy group, benzylcarbonyloxy, o-methylbenzylcarbonyloxy, p-methylbenzylcarbonyloxy, p-chlorobenzylcarbonyloxy, p-fluorobenzylcarbonyloxy, p-methoxybenzylcarbonyloxy, p-nitrobenzylcarbonyloxy, p-cyanobenzylcarbonyloxy, 1-naphthoxymethylcarbonyloxy, 2-naphthoxymethylcarbonyloxy and pyridylmethyloxycarbonyloxy can be mentioned.

As an arylurea group, phenylurea, o-methylphenylurea, p-methylphenylurea, p-chlorophenylurea, p-fluorophenylurea, p-methoxyphenylurea, p-nitrophenylurea, p-cyanophenylurea, 1-naphthylurea and 2-naphthylurea can be mentioned.

As an aryl C_{1-6} alkylurea group, benzylurea, o-methylbenzylurea, p-methylbenzylurea, p-chlorobenzylurea, p-fluorobenzylurea, p-methoxybenzylurea, p-nitrobenzylurea, p-cyanobenzylurea, 1-naphthylmethylurea, 2-naphthylmethylurea and pyridylmethylurea can be mentioned.

As an arylthiourea group, phenylthiourea, o-methylphenylthiourea, p-methylphenylthiourea, p-chlorophenylthiourea, p-fluorophenylthiourea, p-methoxyphenylthiourea, p-nitrophenylthiourea, p-cyanophenylthiourea, 1-naphthylthiourea and 2-naphthylthiourea can be mentioned.

As an aryl C_{1-6} alkylthiourea group, benzylthiourea, o-methylbenylthiourea, p-methylbenzylthiourea, p-chlorobenzylthiourea, p-fluorobenzylthiourea, p-methoxybenzylthiourea, p-nitrobenzylthiourea, p-cyanobenzylthiourea, 1-naphthylmethylthiourea, 2-naphthylmethylthiourea and pyridylmethylthiourea can be mentioned.

If the compound of the formula (1) of the present invention is able to form a pharmaceutically (and/or veterinarily) acceptable salt with an acid, the pharmaceutically (and/or veterinarily) acceptable salt is also able to be used as a active ingredient of the medicine(and/or veterinarily medicine).

As the pharmaceutically (and/or veterinarily) acceptable salt, the salt of an acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, acetic acid, benzoic acid, tartaric acid, phosphoric acie, lactic acid, maleic acid, fumaric acid,

malic acid, gluconic acid or salicylic acid can be mentioned.

As preferable compounds of the present invention, the following compounds can be mentioned.

(1)A benzoxazine derivative of the formula (1), wherein R^1 is a hydrogen atom, a halogen atom, a nitro group, a cyano group, a formyl group, a carboxyl group, a hydroxyl group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group {said C_{1-6} alkylamino group and said di C_{1-6} alkylamino group are unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylurea group, an arylcarbonylamino group, an aryl C_{1-6} alkyl carbonylamino group or an arylurea group {said alkylcarbonylamino group, alkylurea group, arylcarbonylamino group, arylalkyl carbonylamino group and arylurea group are each unsubstituted or substituted by R^7},

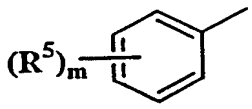
both R^2 and R^3 are a methyl group, and

X is -CONH-, or its pharmaceutically acceptable salt.

(2)A benzoxazine derivative or its pharmaceutically acceptable salt according to (1) mentioned above, wherein R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group {said alkyl group and C_{3-6} cycloalkyl group each are unsubstituted or substituted by R^7}, and

W is $-CH_2-$.

(3) A benzoxazine derivative or its pharmaceutically acceptable salt according to (2) mentioned above, wherein Y is



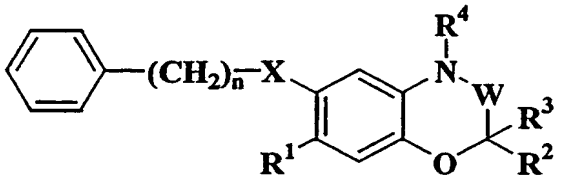
(wherein R^5 is a hydrogen atom, a C_{1-6} alkoxy group (said alkoxy group may be substituted by a halogen atom), a phenyl group (said

phenyl group is unsubstituted or substituted by R^6), a hydroxyl group, a nitro group, a cyano group, a formyl group, a formamido group, an amino group, a C_{1-6} alkylamino group, a C_{1-6} alkoxycarbonyl group or a di C_{1-6} alkylamino group).

(4) A benzoxazine derivative or its pharmaceutically acceptable salt according to (3) mentioned above, wherein R^1 is a hydrogen atom or a nitro group.

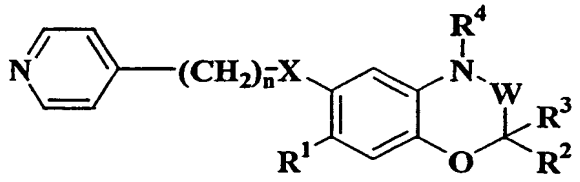
The concrete examples of the compounds which can be used in the present invention will be shown hereunder. However, the present invention is not to be restricted by them. In the specification, "Me" means methyl, "Et" means ethyl, "Pr" means propyl, "Bu" means butyl, "Ac" means acetyl ($COCH_3$) and "-" means a bond.

Table 1



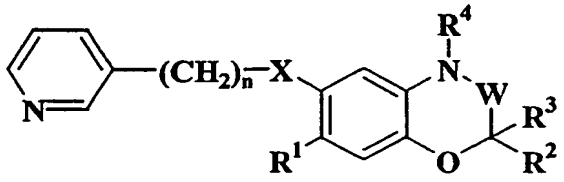
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 2



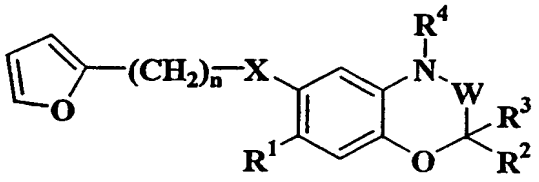
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 3



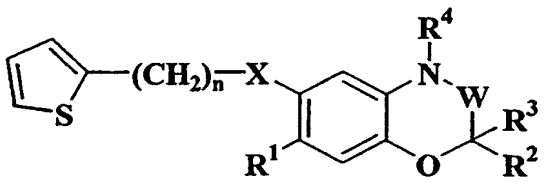
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 4



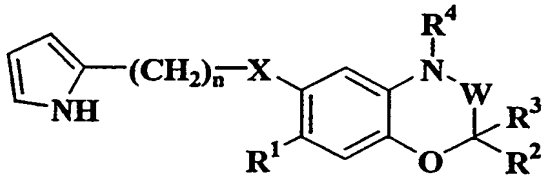
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 5



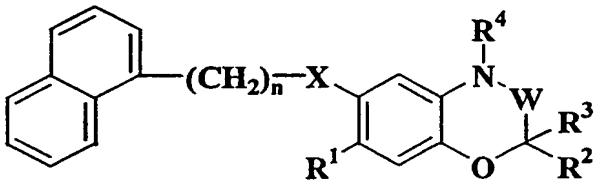
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 6



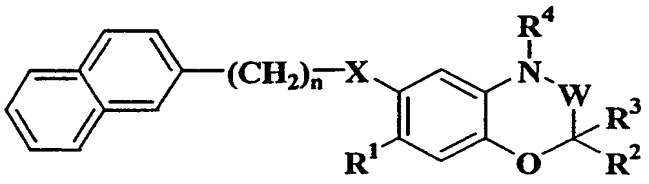
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 7



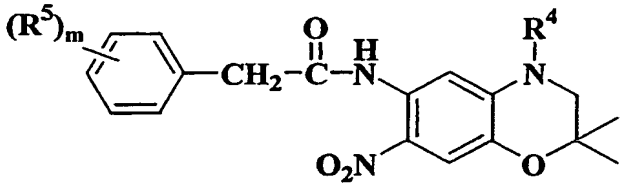
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 8



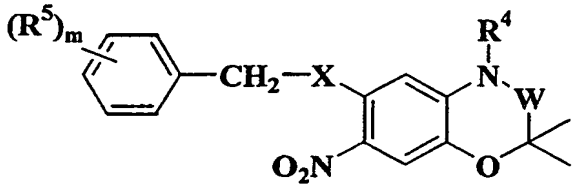
R^1	R^2	R^3	R^4	n	X	W
H	Me	Me	Me	1	CONH	CH_2
F	Me	Me	Me	1	CONH	CH_2
Br	Me	Me	Me	1	CONH	CH_2
Me	Me	Me	Me	1	CONH	CH_2
CF_3	Me	Me	Me	1	CONH	CH_2
OMe	Me	Me	Me	1	CONH	CH_2
c-Pr	Me	Me	Me	1	CONH	CH_2
NO_2	Me	Me	Me	1	CONH	CH_2
CN	Me	Me	Me	1	CONH	CH_2
CHO	Me	Me	Me	1	CONH	CH_2
CO_2H	Me	Me	Me	1	CONH	CH_2
OH	Me	Me	Me	1	CONH	CH_2
CH_2OH	Me	Me	Me	1	CONH	CH_2
NHCHO	Me	Me	Me	1	CONH	CH_2
NH_2	Me	Me	Me	1	CONH	CH_2
NHMe	Me	Me	Me	1	CONH	CH_2
$NHSO_2Me$	Me	Me	Me	1	CONH	CH_2
$CONH_2$	Me	Me	Me	1	CONH	CH_2
CONHMe	Me	Me	Me	1	CONH	CH_2
COMe	Me	Me	Me	1	CONH	CH_2
CO_2Me	Me	Me	Me	1	CONH	CH_2
NO_2	H	H	Me	1	CONH	CH_2
NO_2	Et	Et	Me	1	CONH	CH_2
NO_2	Me	Me	cPr	1	CONH	CH_2
NO_2	Me	Me	Me	2	CONH	CH_2
NO_2	Me	Me	Me	3	CONH	CH_2
NO_2	Me	Me	Me	1	CH_2NH	CH_2
NO_2	Me	Me	Me	1	NHCONH	CH_2
NO_2	Me	Me	Me	1	SO_2NH	CH_2
NO_2	Me	Me	Me	1	CONH	CO

Table 9



R^4	R^5	m
Me	p-OMe	1
Me	p-OEt	1
Me	p-F	1
Me	p-NHMe	1
Me	p-NMe_2	1
Me	p-NO_2	1
Me	p-CN	1
Me	p-Me	1
Me	p-OH	1
Me	p-Cl	1
Me	p-Ac	1
Me	p-CO_2Me	1
Me	m-OMe	1
Me	o-OMe	1
c-Pr	p-OMe	1
c-Pr	p-F	1
c-Pr	p-NHMe	1
c-Pr	p-NO_2	1
c-Pr	p-OH	1
c-Pr	p-Ac	1
c-Pr	p-CO_2Me	1
c-Pr	m-OMe	1
c-Pr	o-OMe	1
Me	p-OMe	1
Et	p-OMe	1
i-Pr	p-OMe	1
Me	m,p-$(OMe)_2$	2
Et	m,p-$(OMe)_2$	2
c-Pr	m,p-$(OMe)_2$	2

Table 10



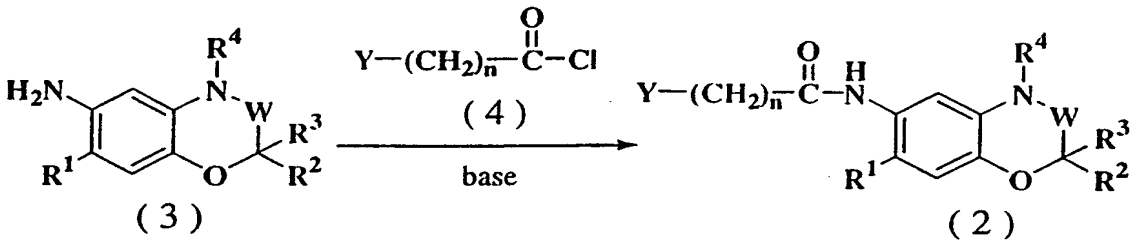
R^4	R^5	m	W	X
Me	p-OMe	1	CH_2	CH_2NH
Me	p-F	1	CH_2	CH_2NH
Me	p-NO_2	1	CH_2	CH_2NH
Me	m,p-$(OMe)_2$	2	CH_2	CH_2NH
Me	p-NHMe	1	CH_2	CH_2NH
Me	p-CO_2Me	1	CH_2	CH_2NH
Me	m-OMe	1	CH_2	CH_2NH
Me	p-OMe	1	CO	CH_2NH
c-Pr	p-OMe	1	CH_2	CH_2NH
Me	p-OMe	1	CH_2	NHCONH
Me	p-F	1	CH_2	NHCONH
Me	p-NO_2	1	CH_2	NHCONH
Me	m,p-$(OMe)_2$	2	CH_2	NHCONH
Me	p-NHMe	1	CH_2	NHCONH
Me	p-CO_2Me	1	CH_2	NHCONH
Me	m-OMe	1	CH_2	NHCONH
Me	p-OMe	1	CO	NHCONH
c-Pr	p-OMe	1	CH_2	NHCONH
Me	p-OMe	1	CH_2	SO_2NH
Me	p-F	1	CH_2	SO_2NH
Me	p-NO_2	1	CH_2	SO_2NH
Me	m,p-$(OMe)_2$	2	CH_2	SO_2NH
Me	p-NHMe	1	CH_2	SO_2NH
Me	p-CO_2Me	1	CH_2	SO_2NH
Me	m-OMe	1	CH_2	SO_2NH
Me	p-OMe	1	CO	SO_2NH
c-Pr	p-OMe	1	CH_2	SO_2NH

(Mode for carrying out the invention)

The methods for producing the compounds of the present invention will be explained in the following.

Of the compounds of the formula (I), the compounds of the formula (2) in which X=-CONH-, as shown in the reaction scheme 1, can be synthesized by reacting a compound of the formula (3) with a acid chloride of the formula (4) in the presence of a base in an inert solvent.

Reaction Scheme 1



As the examples of the solvents used in this reaction, the solvents in the following can be mentioned: sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; and halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane. Preferably, the halogenated hydrocarbons can expediently be used.

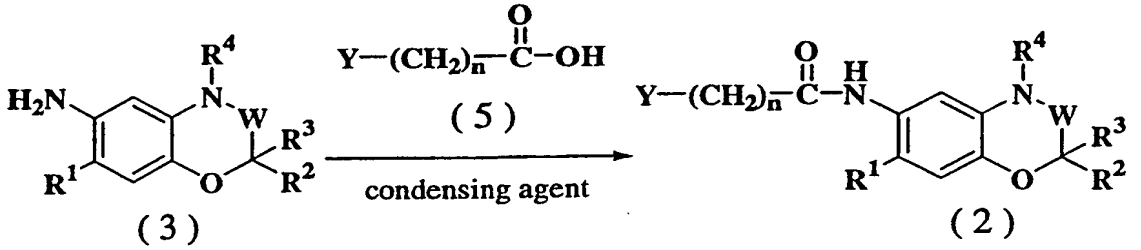
As the bases used in this reaction, trialkylamine such as triethylamine and ethyldiisopropylamine; and pyridines such as pyridine, 2,6-lutidine and 2,6-di-tert-butylpyridine can be mentioned, and triethylamine, ethyldiisopropylamine and pyridine can be preferably mentioned.

The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from -10℃ to +20℃.

The mole ratio of the reactants i.e. the mole number of the compound (4)/ the mole number of the compound (3) is in a range of 0.5～6.0, preferably in a range of 2.0～3.0.

The compounds of the formula (2), as shown in the reaction scheme 2, can also be synthesized by reacting a compound of the formula (3) with a carboxylic acid of the formula (5) using a condensing agent in an inert solvent.

Reaction Scheme 2



(3) (2)

As the examples of the solvents used in this reaction, the solvents in the following can be mentioned: sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; and halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane. Preferably, the halogenated hydrocarbons can expediently be used.

The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from -10℃ to +20℃.

The mole ratio of the reactants i.e. the mole number of the compound (5)/ the mole number of the compound (3) is in a range of 0．5～4．0，preferably in a range of 1．0～2．0．

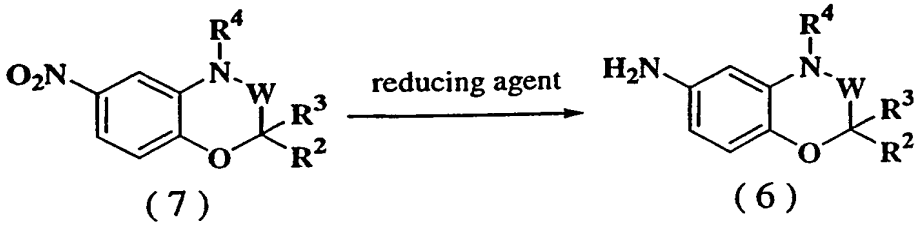
As the condensing agent used, dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-ethyl-N'-3-dimethylaminopropylcarbodiimide, N,N'-carbonyldiimidazole can be mentioned.

Further to one of these condensing agents, N-hydroxysuccinimide, 1-hydroxybenzotriazole, 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine may be added.

Of the compounds of the formula (3), the compounds of the formula (6) in which R^1 is a hydrogen atom, as shown in the reaction

scheme 3, can be synthesized by reducing the nitro group of the compound of the formula (7) using one or more reducing agents.

Reaction Scheme 3

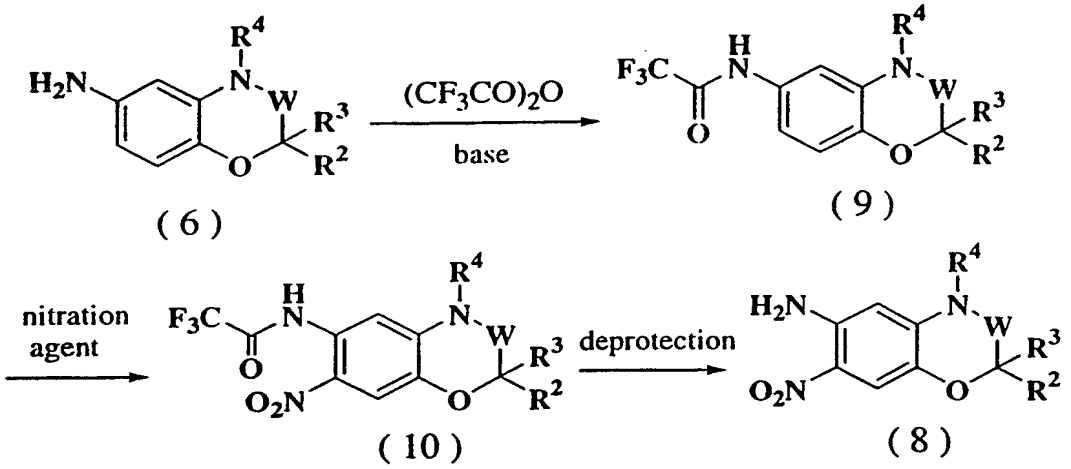


(7) (6)

Of the compounds of the formula (3), the compounds of the formula (8) in which R^1 is a nitro group, as shown in the reaction scheme 4, can be synthesized by using the compound of the formula (6) as a starting material and by using the method similar to one described in Japanese Patent Application Laid-open No. Hei 5-70464.

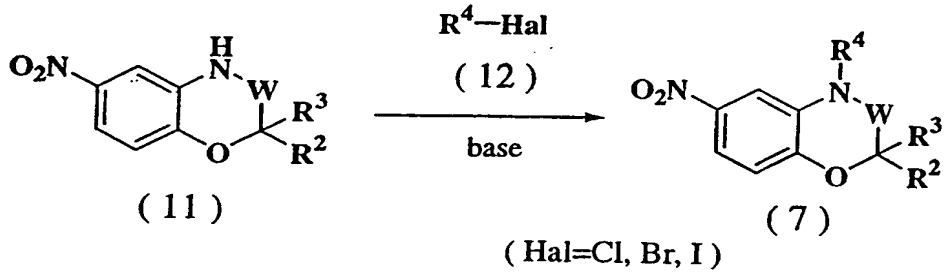
In other words, the compound of the formula (6) is changed into the compound of the formula (9) by using trifluoroacetic anhydride. And the resultant compound of the formula (9) is changed into the compound of the formula (10) by using nitrating reagent and after that the compounds of the formula (8) can be synthesized by deprotection of the compound of the formula (10) under a acidic or basic condition.

Reaction Scheme 4



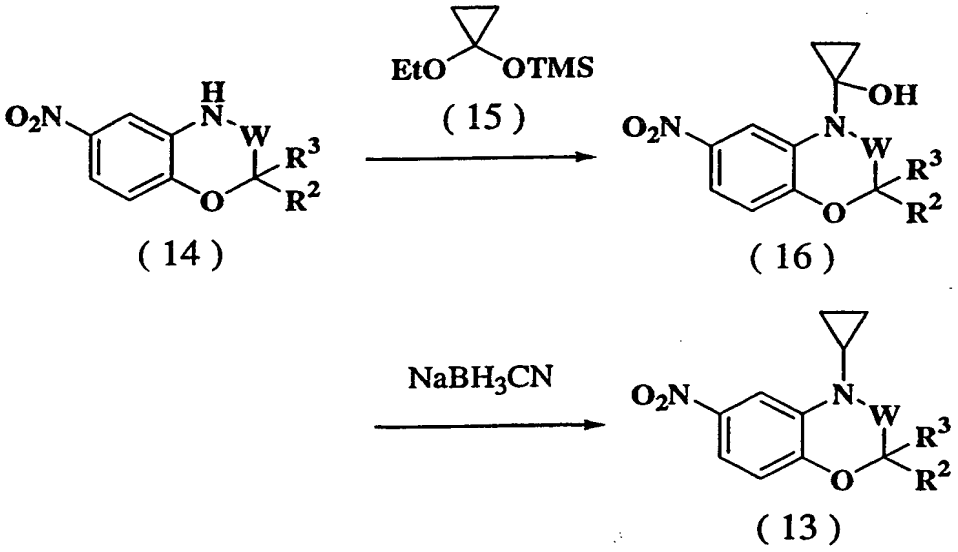
The compounds of the formula (7) in which R^4 is a C_{1-6}alkyl group or C_{3-6}cycloalkyl group, as shown in the reaction scheme 5, can be obtained by reacting the compound of the formula (11) with the halogenated compound of the formula (12) in the presence of a base.

Reaction Scheme 5



Of the compounds of the formula (7), the compounds of the formula (13) in which R^4 is cyclopropyl, as shown in the reaction scheme 6, can be also synthesized according to the preparation method described in Tetrahedron Letters, 36, 7399, (1995) by reducing the compound of the formula (16) (which has been obtained by reacting the compound of the formula (14) with the cyclopropyl compound of the formula (15) in the presence of sodium cyanoborohydride) using sodium cyanoborohydride under acidic condition.

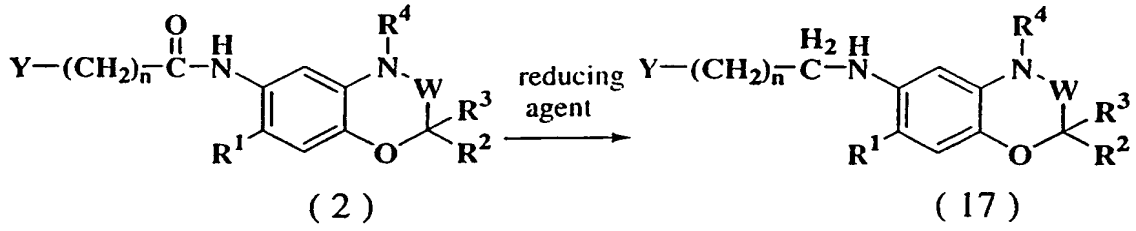
Reaction Scheme 6



The compound of the formula 14), wherein both R^2 and R^3 are methyl can be synthesized by the method described in Chem. Pharm. Bull. , 44, 103, (1996).

Of the compounds of the formula (1), the compounds of the formula (17) in which X is $-CH_2NH-$, as shown in the reaction scheme 7, can be synthesized by reducing the compound of the formula (2) by a reducing agent.

Reaction Scheme 7



As the examples of the reducing agents for reducing the compound of the formula (2) in the reaction scheme 7, lithium aluminum hydride, sodium borohydride, etc. can be mentioned. Preferably, lithium aluminum hydride can be mentioned.

As the examples of the solvents used in the reducing reaction of

the compound of the formula (2), the solvents in the following can be mentioned:

(In the case when sodium borohydride is used as the reducing agent) aromatic hydrocarbons such as benzene and toluene; esters such as ethyl acetate and methyl acetate; sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and alcohols such as methanol, ethanol and propanol; as well as water. Preferably, alcohols can be used.

(In the case when lithium aluminum hydride is used as the reducing agent)

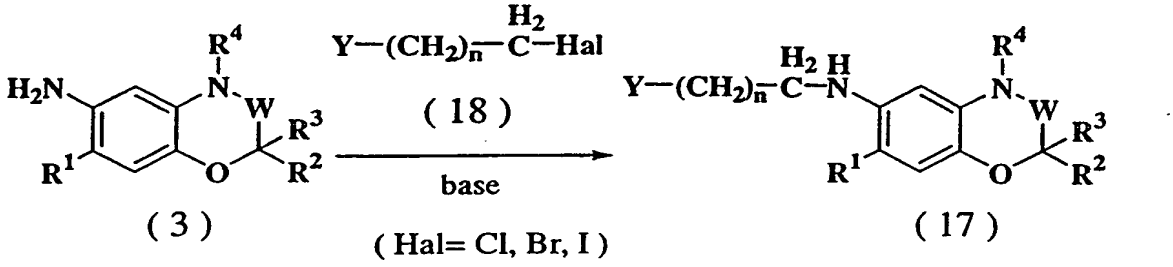
aromatic hydrocarbons such as benzene and toluene; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane. Preferably, the ethers can be used.

The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from -10℃ to +20℃.

The mole ratio of the reactants i.e. the mole number of the reducing agent/ the mole number of the compound (2) is in a range of 0.5～4.0, preferably in a range of 1.0～2.0.

The compounds of the formula (17), as shown in the reaction scheme 8, can be also synthesized by reacting the compound of the formula (3) with the alkyl halide of the formula (18) in the presence of a base.

Reaction Scheme 8



As the examples of the solvents used in the reaction of the compound of the formula (3) with the alkyl halide of the formula (18), the solvents in the following can be mentioned:
aromatic hydrocarbons such as benzene and toluene; esters such as ethyl acetate and methyl acetate; sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and alcohols such as methanol, ethanol and propanol. Preferably, the amides can be expediently used.

The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from 0℃ to the refluxing temperature.

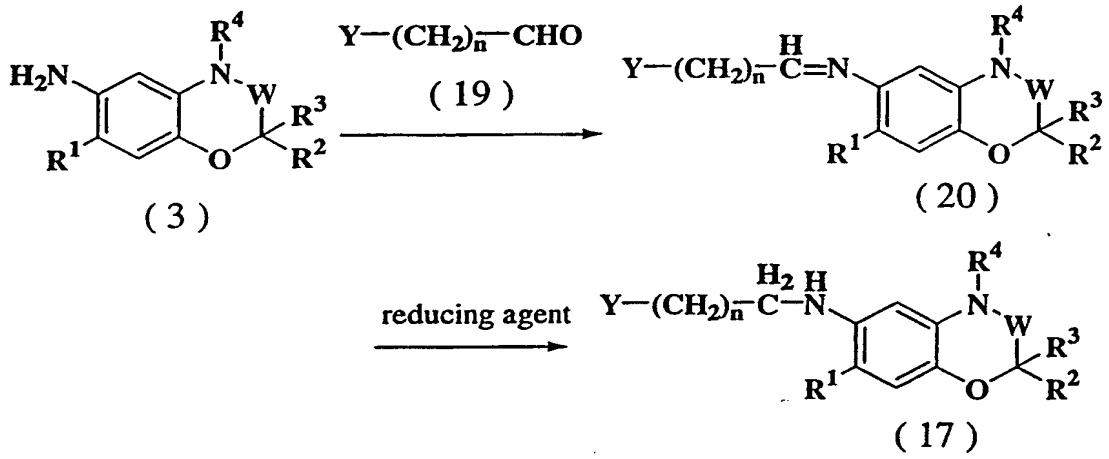
The mole ratio of the reactants i.e. the mole number of the compound (18)/ the mole number of the compound (3) is in a range of 0.5～4.0, preferably in a range of 1.0～2.0.

As the examples of the bases used in the reaction scheme 8, the bases in the following can be mentioned: inorganic bases such as potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, potassium hydroxide and sodium hydroxide; organic bases such as triethylamine, ethyldiisopropylamine, pyridine, 2,6-lutidine, 2,6-di-tert-butylpyridine, N-methylmorpholine and proton sponge. Preferably, triethylamine and ethyldiisopropylamine can be mentioned.

The compounds of the formula (17), as shown in the reaction

scheme 9, can be also obtained by reducing the compound of the formula (20) (which is obtained by the reaction of the formula (3) with an aldehyde of the formula (19)) using a reducing agent.

Reaction Scheme 9



As the examples of the reducing agents for reducing the compound of the formula (20) in the reaction scheme 9, lithium aluminum hydride, sodium borohydride, etc. can be mentioned. Preferably, sodium borohydride can be mentioned.

As the examples of the solvents used in the reducing reaction of the compound of the formula (20), the solvents in the following can be mentioned:

(In the case when sodium borohydride is used as the reducing agent) aromatic hydrocarbons such as benzene and toluene; esters such as ethyl acetate and methyl acetate; sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane; and alcohols such as methanol, ethanol and propanol; as well as water. Preferably, the alcohols can be used.

(In the case when lithium aluminum hydride is used as the reducing agent)

aromatic hydrocarbons such as benzene and toluene; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane. Preferably,

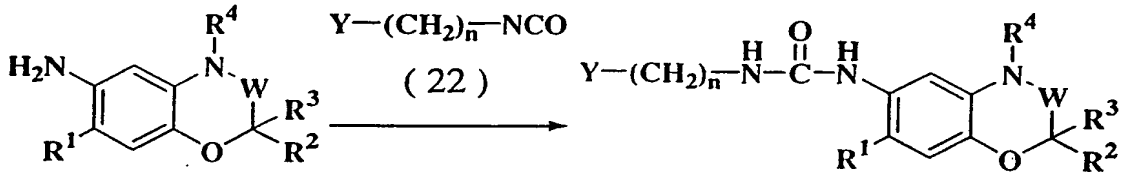
the ethers can be used.

The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from -10℃ to +20℃.

The mole ratio of the reactants i.e. the mole number of the reducing agent/ the mole number of the compound (20) is in a range of 0.5～4.0, preferably in a range of 1.0～2.0.

Of the compound of the formula (1), the compounds of the formula (21) wherein X is -NHCONH-, as shown in the reaction scheme 10, can be obtained by reacting the compound of the formula (3) with the compound of the formula (22).

Reaction Scheme 10



(3) (21)

As the examples of the solvents used for the reaction of the compound of the formula (3) with the compound of the formula (22), the solvents in the following can be mentioned:

aromatic hydrocarbons such as benzene and toluene; esters such as ethyl acetate and methyl acetate; sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; and halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane. Preferably, the amides can be expediently used.

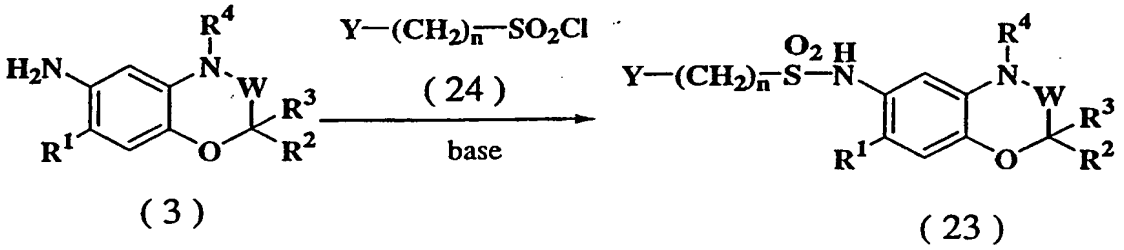
The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from 0℃ to the refluxing temperature.

The mole ratio of the reactants i.e. the mole number of the compound (22)/the mole number of the compound (3) is in a range of

0.5～4.0, preferably in a range of 1.0～2.0.

Of the compound of the formula (I), the compounds of the formula (21) wherein X is $-SO_2NH-$, as shown in the reaction scheme 11, can be obtained by reacting the compound of the formula (3) with the compound of the formula (24) in the presence of a base.

Reaction Scheme 11



(3) (23)

As the examples of the solvents used for the reaction of the compound of the formula (3) with the compound of the formula (24), the solvents in the following can be mentioned:
aromatic hydrocarbons such as benzene and toluene; esters such as ethyl acetate and methyl acetate; sulfoxides such as dimethyl sulfoxide; amides such as dimethylformamide and dimethylacetamide; ethers such as ethyl ether, dimethoxyethane and tetrahydrofurane; and halogenated hydrocarbons such as dichloromethane, chloroform and dichloroethane. Preferably, the amides can be expediently used.

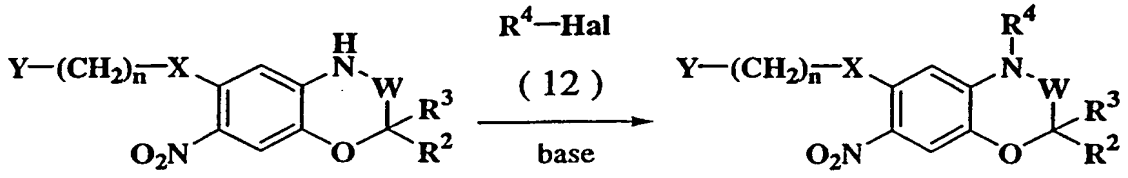
The reaction temperature is usually from -20℃ to the refluxing temperature of the solvent used in this reaction, preferably from 0℃ to 30℃.

The mole ratio of the reactants i.e. the mole number of the compound (24)/the mole number of the compound (3) is in a range of 0.5～4.0, preferably in a range of 1.0～2.0.

The compound of the formula (I) wherein R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group, as shown in the reaction scheme

12, can be obtained by alkylating or cycloalkylating the compound of the formula (25) in the similar method shown in the reaction scheme 5 or 6.

Reaction Scheme 12



(25) (Hal=Cl, Br, I) (I)

The reaction shown in the reaction scheme 12 can be done in the similar conditions to those shown in the reaction scheme 5 or 6.

As mentioned above, we have found that the compounds which are shown in the formula (I), have a strong activity of negative chronotropism.

Since the compounds show a negative chronotropic effect without causing a negative inotropic effect, it is considered that the compounds may have an antianginal effect due to reduction of the amount of cardiac oxygen consumption and of the cardiac work load. In addition, it is also considered that the compounds may have an antiarrhythmic action due to prolongation of the effective refractory period.

Therefore, it is expected that the compounds from the present invention are useful for the treatment of cardiovascular disorders which are concerned in abnormalities of oxygen consumption and/or energy metabolism, and also for the treatment of other cardiac disorders which are effective by reduction of heart rate.

For example, the compound from the present invention are useful for the treatment of heart failure of mammals including human beings, and for the treatment of cardiovascular disorders which will make progress toward heart failure, for example, ischemic heart disease, retention of fluid, pulmonary hypertension, valvular disease,

congenital heart disease, myocardial disease, pulmonary edema, exertional angina, myocardial infarction, arrhythmia and atrial fibrillation/flutter.

The present invention provides pharmaceutical compositions containing an effective amount of the compounds of the formula (I) for curing these diseases.

As the manner of administration of the compounds of the present invention, there may be mentioned parenterally administration by injections (subcutaneous, intraveneous, intramuscular or intraperitoneal injection), ointments, suppositories or aerosols, or an oral administration in the form of tablets, capsules, granules, pills, syrups, liquids, emulsions or suspensions.

The above pharmaceutical or veterinary composition of the present invention contains at least one compound of the present invention in a total amount of from about 0.01 to 99.5 % by weight, preferably from about 0.1 to 30 % by weight, based on the total weight of the composition.

In addition to the compound(s) of the present invention or to the compositions containing the present compound(s), another or other pharmaceutically or veterinarily active compounds may be incorporated. Further, the compositions of the present invention may contain a plurality of the compounds of the present invention.

The clinical dose of the compound of the present invention varies depending upon the age, the body weight, the sensitivity or the sympton, etc. of the patient. In general, however, the effective daily dose is usually from about 0.003 to 1.5 g, preferably from about 0.01 to 0.6 g for an adult. If necessary, however, an amount outside the above range may be administered.

The compound of the present invention may be prepared into various suitable formulations depending upon the manner of administration, in accordance with conventional methods commonly employed for the preparations of pharmaceutical formulations.

Namely, tablets, capsules, granules or pills for oral administration, may be prepared by using excipients such as white sugar, lactose, glucose, starch or mannitol; binders such as hydroxypropyl cellulose, syrups, arabic gum, gelatin, sorbitol, tragacanth gum, methyl cellulose or polyvinylpyrrolidone; disintegrants such as starch, carboxymethyl cellulose (CMC) or its calcium salt, crystal cellulose powder or polyethylene glycol (PEG); lubricants such as talc, magnesium or calcium stearate, silica; and smoothers such as sodium laurate, glycerol, etc.

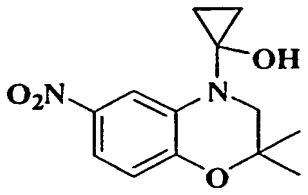
The injections, solutions (liquids), emulsions, suspensions, syrups or aerosols may be prepared using a solvent for the active ingredient such as water, ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol or polyethylene glycol; surfactants such as sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene ether of hydrogenated castor oil, lecithin; suspending agents such as cellulose derivatives such as sodium salt of carboxymethyl cellulose derivatives such as methyl cellulose or natural rubbers such as tragacanth or arabic gum; or preservatives such as para-hydroxybenzoic acid, benzalkonium chloride, salts of sorbic acid, etc.

Ointments which are an endermic preparation may be prepared by using, e.g., white vaseline, liquid paraffin, higher alcohols, Macrogol ointment, hydrophilic ointment base or hydrogel base, etc.

The suppositories may be prepared by using, e.g., cacao butter, polyethylene glycol, lanolin, fatty acid triglycerides, coconut oil, polysorbate, etc.

Now, the present invention is explained referring to examples, but it is not to be limited to these examples.

Reference Example 1: Synthesis of 3,4-dihydro-2,2-dimethyl-4-(1-hydroxycyclopropyl)-6-nitro-2H-1,4-benzoxazine.



To a solution of 3,4-dihydro-2,2-dimethyl-6-nitro-2H-1,4-benzoxazine (which was synthesized according to Matsumoto. Y et al. Chem. Pharm. Bull., 44(1), 103, (1996) (4.0 g, 16 mmol) , acetic acid (9.2 mL, 10 eq)、molecular sieves 3 Å (4.0 g) and [(1-ethoxycyclopropyl)oxy]trimethylsilane (19 mL, 6.0 eq) in methanol (80 mL), sodium cyanoborohydride (4.0 g, 4.0 eq)was added at 0℃, and after the reaction mixture had been stirred at 0℃ for 1.5 hours, this mixture was heated under reflux for 21 hours.

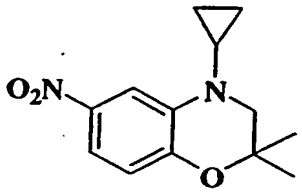
After the filtration of the reaction mixture, the filtrate was concentrated and an aqueous 1N-sodium hydroxide solution was added to the resultant residue and the mixture of the residue was extracted with ethyl acetate. And the organic layer obtained was washed with brine and was dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure, and the residue obtained was purified by silica gel column chromatography (eluent, hexane : etyl acetate = 5 : 1) and recrystallized from ethyl acetate/hexane to give the title compound (2.9 g, 73 %, m.p. 135.2 – 135.5 ℃) as orange crystals.

^{1}H NMR ($CDCl_3$) δ : 1.06-1.32 (m, 10H), 2.99 (bs, 1H), 3.26 (s, 2H), 6.82 (d, J = 9 Hz, 1H), 7.68 (dd, J = 3 Hz, 9 Hz, 1H), 8.01 (d, J = 3 Hz, 1H).

MS (FAB) m/z 247 (bp) , 265 $[M+H]^+$.

Reference example 2: Synthesis of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-6-nitro-2H-1,4-benzoxazine



To a solution of 3,4-dihydro-2,2-dimethyl-4-(1-hydroxycyclopropyl)-6-nitro-2H-1,4-benzoxazine (3.32 g, 12.6 mmol) in methnol (66 mL), sodium cyanoborohydride (5.1 g, 4.0 eq) and acetic acid (6.3 mL, 9.0 eq) were added at room temperature, and the reaction mixture was stirred at room temperature for 7 days.

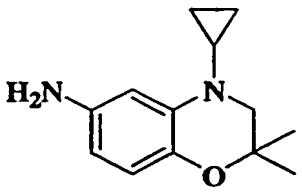
After the solvent had been distilled off the reaction mixture under reduced pressure, an aqueous 1N-sodium hydroxide solution was added to the residue obtained and the resultant mixture was extracted with ethyl acetate. The organic layer was washed with brine and was dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, hexane : etyl acetate = 10 : 1) and the yellow solid obtained was recrystallized from ethyl acetate/hexane to give the title compound (2.0 g, 62 %, m.p. 77.1－77.5 ℃) as yellow crystals.

^{1}H NMR ($CDCl_3$) δ : 0.54-1.12 (m, 4H), 1.32 (s, 6H), 2.25-2.58 (m, 1H), 3.05 (s, 2H), 6.73 (d, J = 9 Hz, 1H), 7.61 (dd, J = 2 Hz, 9 Hz, 1H), 7.97 (d, J = 2 Hz, 1H).

MS (EI) m/z 219 (bp), 248 [M^+].

Reference example 3: Synthesis of 6-amino-4-cyclopropyl-3,4-dihydro-2,2-dimethyl-2H-1,4-benzoxazine



To a solution of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-6-

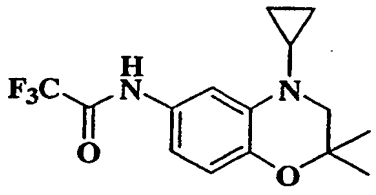
nitro-2H-1,4-benzoxazine (51 mg, 0.21 mmol) in ethanol (1 mL), a catalytic amount of Raney nickel was added and the reaction mixture was stirred under hydrogen at room temperature for 23 hours.

After the filtration of the reaction mixture with Celite, the solvent was evaporated under reduced pressure and the residue obtained was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to obtain the title compound (39 mg, 85 %) as a black oily substance.

^{1}H NMR ($CDCl_3$) δ : 0.58-0.88 (m, 4H), 1.25 (s, 6H), 2.05-2.37 (m, 1H), 2.95 (s, 2H), 3.28 (bs, 2H), 5.91-6.10 (m, 1H), 6.45-6.59 (m, 2H).

MS (EI) m/z 202 , 218 [M^+], (bp) .

Reference example 4: Synthesis of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-6-trifluoroacetamide-2H-1,4-benzoxazine



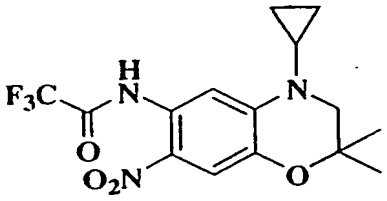
To a solution of 6-amino-4-cyclopropyl-3,4-dihydro-2,2-dimethyl-2H-1,4-benzoxazine (39 mg, 0.18 mmol) and triethylamine (0.03 mL, 1 eq) in dichloromethane (0.3 mL), a solution of trifluoroacetic anhydride (0.03 mL, 1 eq) in dichloromethane (0.1 mL) was added at 0℃, and the reaction mixture was stirred at 0℃ for 90 minutes.

After addition of water to the reaction mixture, the resultant mixture was extracted with chloroform and the organic layer obtained was then dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to obtain the title compound (35 mg, 62 %) as a clear brown oily substance.

^{1}H NMR ($CDCl_3$) δ : 0.57-0.60 (m, 2H), 0.84-0.89 (m, 2H), 1.29 (s, 6H), 2.30-2.35 (m, 1H) ,3.01 (s, 2H), 6.72 (d, J = 8 Hz, 1H), 6.78 (dd, J = 3 Hz, 8 Hz, 1H) , 7.47 (d, J = 3 Hz, 1H), 7.85 (bs, 1H).
MS (EI) m/z 202 (bp), 314 [M^+] .

Reference example 5: Synthesis of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-7-nitro-6-trifluoroacetamide-2H-1,4-benzoxazine

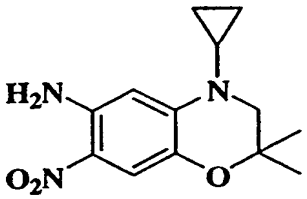


To a solution of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-6-trifluoroacetamide-2H-1,4-benzoxazine (0.20 g, 0.63 mmol) in acetic acid (0.90 mL) , a solution of fuming nitric acid (0.034 mL) in acetic acid (0.50 mL) was added and the reaction mixture was stirred at room temperature for 35 minutes.

The reaction mixture was diluted with ethyl acetate and then neutralized with an aqueous saturated sodium bicarbonate solution and then the resultant mixture was separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 10 : 1) to obtain a product of the title compound, and the product was recrystallized from ethyl acetate/hexane to obtain the title compound (57 mg, 25 %, m.p. 87-90 ℃) as orange crystals.
^{1}H NMR ($CDCl_3$) δ : 0.69-0.73 (m, 2H), 1.05-1.10 (m, 2H), 1.38 (s, 6H), 2.63-2.70 (m, 1H), 3.22 (s, 2H), 7.69 (s, 1H), 8.51 (s, 1H), 12.00 (bs, 1H).
MS (FAB) m/z 344, 360 [M+H]$^+$, (bp) .

Reference Example 6: Synthesis of 6-amino-4-cyclopropyl-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1,4-benzoxazine



To a mixed suspension of 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-7-nitro-6-trifluoroacetamide-2H-1,4-benzoxazine (32 mg, 0.089 mmol) in water (0.07 mL) and methnol (0.74 mL), sodium bicarbonate (15 mg, 2.0 eq) was added and the reaction mixed suspension was stirred at room temperature for 26 hours.

The reaction mixture was dilued with water and extracted with ethyl acetate. The organic layer was washed with brine and then dried over anhydrous sodium sulfate.

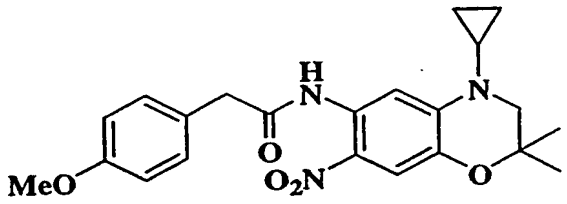
The solvent was evaporated under reduced pressure and the residue was purified by silica gel thin layer chromatography (eluent, hexane : ethyl acetate = 2 : 1) to obtain the title compound (12 mg, 51 %) as an orange solid.

^{1}H NMR ($CDCl_3$) δ : 0.64-0.68 (m, 2H), 0.92-0.96 (m, 2H), 1.25 (s, 6H), 2.50-2.55 (m, 1H), 3.13 (s, 2H), 6.03 (bs, 2H), 6.29 (d, J = 2 Hz, 1H), 7.51 (d, J = 2 Hz, 1H).

MS (FAB) m/z 248, 264 $[M+H]^+$, (bp) .

[Synthesis example]

Synthesis example 1: 4-cyclopropyl-3,4-dihydro-2,2-dimethyl-6-(4'-methoxyphenylacetylamino)-7-nitro-2H-1,4-benzoxazine



To a solution of 6-amino-4-cyclopropyl-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1,4-benzoxazine (96 mg, 0.36 mmol) and diisopropylethylamine (0.25 mL, 4.0eq) in chloroform (0.86 mL), 4-

methoxyphenylacetyl chloride (0.17 mL, 3.0 eq) was added at 0℃ and the reaction mixture was stirred at room temperature for 3 hours.

Water was added to the reaction mixture and the resultant mixture was then extracted with ethyl acetate. And the organic layer obtained was washed with brine and was then dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 3 : 1) to obtain the title compound (0.14 g, 95 %) as an orange oily substance.

^{1}H NMR ($CDCl_3$) δ : 0.67-0.68 (m, 2H), 1.01-1.05 (m, 2H), 1.25 (s, 6H), 2.60-2.63 (m, 1H), 3.16 (s, 2H), 3.73 (s, 2H), 3.81 (s, 3H), 6.93 (d, J = 9 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.60 (s, 1H), 8.60 (s, 1H), 10.85 (bs, 1H).

MS (EI) m/z 394 (bp), 411 [M^+] .

FORMULATION EXAMPLE 1

Formulation of Tablets:

The compound of the present invention	100 g
Lactose	240 g
Crystal cellulose powder	580 g
Corn starch	330 g
Hydroxypropyl cellulose	80 g
CMC-Ca	140 g
Magnesium stearate	30 g
Total	1500 g

The above-mentioned components were mixed by a usual method and then tabletted to produce 10000 sugar-coated tablets, each containing 10 mg of the compound of the present invention as the active ingredient.

FORMULATION EXAMPLE 2

Formulation of Capsules:

The compound of the present invention	100 g

Lactose	400 g
Crystal cellulose powder	950 g
Magnesium stearate	50 g
Total	1500 g

The above-mentioned components were mixed by a usual method and then packed in gelatin capsules to obtain 10000 capsules, each containing 10 mg of the compound of the present invention as the active ingredient.

FORMULATION EXAMPLE 3

Formulation of Soft Capsules:

The compound of the present invention	100 g
PEG 400	444 g
Saturated fatty acid triglyceride	1,445 g
Peppermint oil	1 g
Polysorbate 80	10 g
Total	2,000 g

The above-mentioned components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 10000 soft capsules, each containing 10 mg of the compound of the present invention as the active ingredient.

FORMULATION EXAMPLE 4

Formulation of Ointment:

The compound of the present invention	1.0 g
Liquid paraffin	10.0 g
Cetanol	20.0 g
White vaseline	68.4 g
Ethyl paraben	0.1 g
l-menthol	0.5 g
Total	100.0 g

The above-mentioned components were mixed by a usual method to obtain 1% ointment.

FORMULATION EXAMPLE 5

Formulation of Suppositories:	
the compound of the present invention	10 g
Witepsol H15*	475 g
Witepsol W35*	514 g
Polysorbate 80	1 g
Total	1,000 g

(* Trade name for triglyceride compound)

The above-mentioned components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 1000 suppositories of 1 g, each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6

Formulation of Injection:

The compound of the present invention	1 mg
Distilled water for injection	5 ml

The formulation is prepared by dissolving the compound in distilled water whenever it is required.

[PHARMACOLOGICAL TEST EXAMPLES]

Effect on heart rate

METHODS

The heart of male Hartlay guinea-pigs was isolated and the right atrium dissected in an aqueous Krebs Henseleit solution aerated with 95% O_2/5% CO_2. Specimens were suspended in an FD pickup in an organ bath filled with nutrient broth at 31□C, and a 1 g resting tension was applied.

The maximum reaction was determined by cumulatively adding isoproterenol to the specimens after achieving equilibrium while changing nutrient broth. After washing off isoproterenol and 60 min equalization while changing nutrient broth, each of the compounds were applied to the specimens to determine their effects. The effect of each test compound (10, 30, 100 and 300 μM) was determined as

percentage of the previously determined effect of isoproterenol.

RESULTS

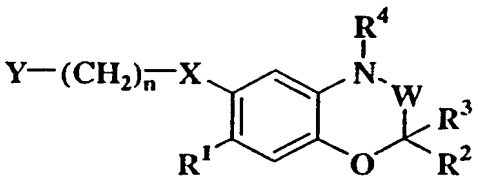
The compounds of the present invention decreased, in a concentration-dependent manner, heart rate.

Industrial applicability

The compounds of the present invention cause a negative chronotropic effect which are useful for improvement of cardiac functions. The present invention provides beneficial drugs for the treatment of heart failure.

CLAIMS

1. A benzoxazine derivative of the formula (I)



(I)

[in which, R^1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group {said alkyl group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkoxy group {said alkoxy group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a phenyl group (said phenyl group is unsubstituted or substituted by R^6 (said R^6 is a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group)), a formyl group, a cyano group or a nitro group}, a C_{3-6} cycloalkyl group {said cycloalkyl group is unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a nitro group, a cyano group, a formyl group, a carboxyl group, a hydroxyl group, a formamido group, a cyanamide group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group {said alkylamino group and di C_{1-6} alkylamino group are unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkylcarbonyloxy group, a C_{1-6} alkylurea group, a C_{1-6} alkylthiourea group, an aryl C_{1-6} alkylamino group, a di(aryl C_{1-6} alkyl)amino group, an arylcarbonylamino group, an aryl C_{1-6} alkylcarbonylamino group, an arylsulfonylamino group, an aryl C_{1-6} alkylsulfonylamino group, an

aryl C_{1-6} alkylaminocarbonyl group, a di(aryl C_{1-6} alkyl)aminocarbonyl group, an arylcarbonyl group, an aryl C_{1-6} alkylcarbonyl group, an aryloxycarbonyl group, an aryl C_{1-6} alkyloxycarbonyl group, an arylcarbonyloxy group, an aryl C_{1-6} alkylcarbonyloxy group, an arylurea group, an aryl C_{1-6} alkylurea group, an arylthiourea group or an aryl C_{1-6} alkylthiourea group {said arylalkylamino group, di(arylalkyl)amino group, arylcarbonylamino group, arylalkylcarbonylamino group, arylsulfonylamino group, arylalkylsulfonylamino group, arylalkylaminocarbonyl group, di(arylalkyl)aminocarbonyl group, arylcarbonyl group, arylalkylcarbonyl group, aryloxycarbonyl group, arylalkyloxycarbonyl group, arylcarbonyloxy group, arylalkylcarbonyloxy group, arylurea group, arylalkylurea group, arylthiourea group and aryl alkylthiourean group each are unsubstituted or substituted by R^7 (said R^7 is a halogen atom, a carboxyl group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a C_{1-6} alkoxy group, a phenyl group (said phenyl group is unsubstituted or substituted by R^6), a formyl group, a cyano group or a nitro group)},

R^2 and R^3 each independently are a hydrogen atom or a C_{1-6} alkyl group {said alkyl group is unsubstituted or substituted by a halogen atom, a C_{1-6} alkoxy group or a hydroxyl group} ,

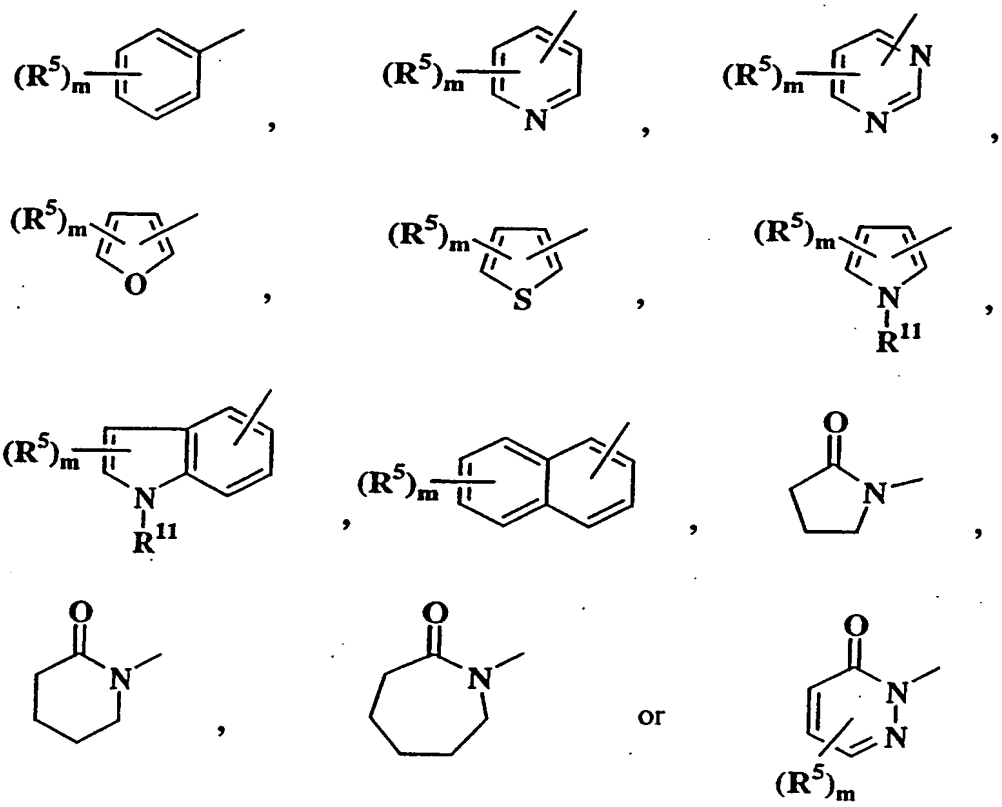
R^4 is a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group {said alkyl group and cycloalkyl group each are unsubstituted or substituted by R^7} , a phenyl group {said phenyl group is unsubstituted or substituted by R^6}, $C(=Y^1)Z^1R^8$ or $C(=Y^1)R^8$ {Y^1 is a oxygen atom, a sulfur atom, or NR^9 (R^9 is a hydrogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group), Z^1 is a oxygen atom, a sulfur atom or NR^{10} (R^{10} is a C_{1-6} alkyl group), R^8 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkenyl group, a C_{1-6} alkynylgroup, a C_{3-6} cycloalkyl group (said alkyl group, alkenyl group, alkynyl group and cycloalkyl group each are unsubstituted or substituted by R^7) or a phenyl group (said phenyl group is unsubstituted or substituted by R^6) } ,

n is 0 or an integer of 1 to four,

W is C=O or $-CH_2-$,

X is $-CONH-$, $-CH_2NH-$, $-NHCONH-$ or $-SO_2NH-$,

Y is



(in which, R^5 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group (said alkyl group is unsubstituted or substituted by a halogen atom or a C_{1-6} alkoxy group), a C_{1-6} alkoxy group (said alkoxy group is unsubstituted or substituted by a halogen atom), a phenyl group (said phenyl group is unsubstituted or substituted by R^6), a hydroxyl group, a nitro group, a cyano group, a formyl group, a formamido group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group, a C_{1-6} alkylcarbonylaminogroup, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkylcarbonyloxy group, a aminosulfonyl group, a C_{1-6} alkylsulfonyl group, a carboxyl group or an arylcarbonyl group,

m is integer of 1 to three, and

R^{11} represents the same meaning as R^{10})}, or its pharmaceutically acceptable salt.

2. A benzoxazine derivative or its pharmaceutically acceptable salt according to claim 1, wherein R^1 is a hydrogen atom, a halogen atom, a nitro group, a cyano group, a formyl group, a carboxyl group, a hydroxyl group, an amino group, a C_{1-6} alkylamino group, a di C_{1-6} alkylamino group {said C_{1-6} alkylamino group and said di C_{1-6} alkylamino group are unsubstituted or substituted by a halogen atom, a carboxyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group, a hydroxyl group, a formyl group, a cyano group or a nitro group}, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylurea group, an arylcarbonylamino group, an aryl C_{1-6} alkyl carbonylamino group or an arylurea group {said alkylcarbonylamino group, alkylurea group, arylcarbonylamino group, arylalkyl carbonylamino group and arylurea group are each unsubstituted or substituted by R^7},

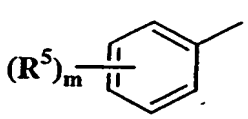
both R^2 and R^3 are methyl group, and

X is -CONH-.

3. A benzoxazine derivative or its pharmaceutically acceptable salt according to claim 2, wherein R^4 is a C_{1-6} alkyl group or a C_{3-6} cycloalkyl group {said alkyl group and C_{3-6} cycloalkyl group each are unsubstituted or substituted by R^7}, and

W is $-CH_2-$.

4. A benzoxazine derivative or its pharmaceutically acceptable salt according to claim 3, wherein Y is



(wherein R^5 is a hydrogen atom, a C_{1-6} alkoxy group (said alkoxy group may be substituted by a halogen atom), a phenyl group (said

phenyl group is unsubstituted or substituted

by R^6), a hydroxyl group, a nitro group, a cyano group, a formyl group, a formamido group, an amino group, a C_{1-6} alkylamino group, a C_{1-6} alkoxycarbonyl group or a di C_{1-6} alkylamino group).

5. A benzoxazine derivative or its pharmaceutically acceptable salt according to claim 4, wherein R^1 is a hydrogen atom or a nitro group.

6. A pharmaceutical composition comprising an active ingredient at least one benzoxazine derivative and/or its pharmaceutically acceptable salt according to any one of claims from 1 to 5.

7. A pharmaceutical composition for curing cardiac insufficiency comprising as an active ingredient at least one benzoxazine derivative and/or its pharmaceutically acceptable salt according to any one of claims from 1 to 5.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/JP 99/04631

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/36 C07D413/12 A61K31/538

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 25 09 155 A (HOECHST AG) 9 September 1976 (1976-09-09) the whole document	1-7
A	WO 97 26243 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); LIU GANG (US); SHAW KENNETH (U) 24 July 1997 (1997-07-24) page 35 -page 36; claims	1-7
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 1999	19/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chouly, J

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INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/JP 99/04631

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 602 458 A (SS PHARMACEUTICAL CO) 22 June 1994 (1994-06-22) claims & JP 06 220029 A cited in the application	1-7
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P,A	MATSUMOTO Y. ET AL: "Novel potassium channel activators" CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 47, no. 7, 1999, pages 971-979, XP002121138 PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP ISSN: 0009-2363 the whole document	1-7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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